UNITED STAT[redacted]EPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/060,294	04/15/98	JENSEN	M	P60953US1

HM12/0120

JACOBSON PRICE
HOLMAN AND STERN
THE JENIFER BUILDING
400 SEVENTH STREET NW
WASHINGTON DC 20004

EXAMINER	
ROMEO,D	

ART UNIT	PAPER NUMBER
1646	12

DATE MAILED: 01/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/060,294	Jensen et al.
Examiner	**Group Art Unit**
David S. Romeo	1646

☒ Responsive to communication(s) filed on *2 Sep 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-49* is/are pending in the application.

Of the above, claim(s) *29-31, 33-39, 46, 48, and 49* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-28, 32, 40-45, and 47* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-49* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-28, 32, 40-45, 47, in Paper No. 11 is acknowledged. The traversal is on the ground(s) that there is a lack of distinctiveness on the part of groups I, IV and V. This is not found persuasive because an application may properly be required to be restricted to one of two or more claimed invention if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (j)) or distinct (MPEP § 806.05 - § 806.05(i)). The Examiner has shown that the inventions are distinct in the last Office action. Furthermore, M.P.E.P. § 803 provides that the separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a *prima facie* case that the search and examination of the plural inventions would impose a serious burden upon the Examiner; such separate classification was set forth in the last Office action.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 29-31, 33-39, 46, 48, 49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 11.

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on 04/15/97. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

4. The abstract of the disclosure is objected to because it is not a single paragraph. Correction is required. See MPEP § 608.01(b).

5. The application is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. The specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See pages 37, 43, Figures-3a, -3b, -4b. This list is not meant to be exhaustive. Each disclosure of a nucleotide or amino sequence requires a separate identifier. Applicant may bring the Figures into compliance by amending either the Figures or the "Brief Description of the Drawings" to recite the appropriate sequence identifier.

Correction is required.

6. Claims 20-25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the

claim(s) in independent form. The DNA of claims 20-25 does not infringe the modified TNFα molecule of claim 1.

7. Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitation antibodies raised in a suitable host wherein the suitable host is a non-human suitable host (claim 3) does not infringe antibodies raised in human host (claim 1).

8. Claims 17 and 18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. A modified TNFα molecule with an inserted T cell epitope (claims 17 and 18), wherein no amino acids are substituted, does not infringe a modified TNFα molecule wherein a fragment has been substituted by a T cell epitope (claim 1).

9. Claim 25 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim 25 not been further treated on the merits.

10. Claim 43 is objected to because of the following informalities: "wherein" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

11. Claim(s) 43 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine for the treatment of TNFα-mediated inflammatory diseases, does not reasonably provide enablement for a vaccine for the treatment of cancer, disseminated sclerosis, psoriasis, osteoporosis, or asthma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are drawn to a vaccine for the treatment of cancer, disseminated sclerosis, psoriasis, osteoporosis, or asthma, which requires that the vaccine be capable of such a use. However, there is nothing in the instant specification or in the prior art of record to suggest that cancer, disseminated sclerosis, psoriasis, osteoporosis, or asthma are diseases promoted by the release or activity of TNFα or that such diseases could be treated with a TNFα vaccine. There are no working examples or guidance for such treatment. It is entirely

unclear how the treatment of cancer could be achieved with a vaccine designed to neutralize TNFα activity, thereby neutralizing the host's tumor/cancer necrosis activity. Neither the prior art of record nor the instant specification establish a nexus between release or activity of TNFα and the development of cancer, disseminated sclerosis, psoriasis, osteoporosis, or asthma, which suggest there is a lack of predictability in the art in the treatment of such diseases with the vaccine of the instant invention. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art, it would require undue experimentation for the skilled artisan to make and use the full scope of the claimed invention.

12. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-28, 32, 40-45, 47 are indefinite over the recitation of "modified human TNFα molecule" because the nature and the extent of the modification are unclear. The metes and bounds of the claim(s) are not clearly set forth. It is suggested that the claim 1 recite "a modified human TNFα molecule ... wherein the modification is ...".

Claims 1-28, 32, 40-45, 47 are indefinite over the recitation of "known to contain" (claim 1) or "known to be immunogenic" (claim 17) because it is unclear what or which persons possess

this knowledge or when it is possessed. The metes and bounds of the claim(s) are not clearly set forth. It is suggested that claim 1 recite "peptide containing an immunodominant T cell epitope".

Claim 1 is indefinite over the recitation of "in any one of ... and/or". The Markush group is recited in an improper Markush format. When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper. See M.P.E.P. 2173.05(h). The metes and bounds of the Markush group are not clearly set forth. It is suggested that the term "or" be used instead of the term "and/or".

The term "substantial change" in claim 1 is a relative term which renders the claim indefinite. The term "substantial change" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 18 is indefinite over the recitation of "derived from" because the nature and the extent of derivation are unclear. The metes and bounds of the claim(s) are not clearly set forth.

Claims 43-45 are indefinite because the members of the Markush group are recited in an improper Markush format. When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a

proper limitation, then "wherein R is A, B, C or D" shall also be considered proper. See M.P.E.P. 2173.05(h). The metes and bounds of the Markush group are not clearly set forth. It is suggested that the claims recite "or" instead of "and", "disease is" instead of "diseases are", and that claim 28 be amended to recite "a disease" instead of "diseases".

Regarding claims 8-11, 18 the phrase "preferably" renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. Description of examples or preferences is properly set forth in the specification rather than the claims. See MPEP § 2173.05(d).

The term "promiscuous" in claims 17 and 18 is a relative term which renders the claim indefinite. The term "promiscuous" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 42 is indefinite over the recitation of "iscom" because acronyms are arbitrarily assigned and their meaning is ambiguous. It is suggested that the acronym be spelled out.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-28, 32, 40-45, 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mouritsen et al. (AV, cited by Applicants) in view of Pennica et al. (BP, cited by Applicants), Shirai et al. (BN, cited by Applicants), or Wang et al. (BL, cited by Applicants), further in view of Jones et al. (BF, cited by Applicants), and/or further in view of Panina-Bordigon et al. (BO, cited by Applicants).

Mouritsen et al. teach a modified mouse TNFα molecules wherein at least one peptide fragment of the mouse TNFα molecule has been substituted by at least one peptide known to contain an immunodominant T cell epitope wherein the substitution introduces a substantial change in the amino acid sequence of the B strand of the front β-sheet (page 10, line 8, through page 11, line 12). Substitutions in this region detoxify the recombinant protein (page 12, lines 16-17). Toxic self proteins such as TNFα can be simultaneously detoxified by removing or mutating biologically active protein segments (page 7, lines 11-15). The modified TNFα could be administered as an anti-TNFα vaccine to patients suffering from diseases where TNFα is important for the pathogenesis (claims 28, 43-45) (page 14, lines 13-20, 26-30; paragraph bridging pages 14-15); the intended use of the vaccine (claims 28, 43-45) has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites an intended use. The modified TNFα

would have at least one of the properties recited in claim 3. The substitutions in the mr103 and mr106 modified human TNFα molecules have been made in the regions of the TNFα molecule so as to essentially preserve the β-sheet structure of the B and G strands. The substitutions essentially preserve the β-sheet structure of any of the strands of the back β-sheet. The mr106 mutant meets the limitations of claim 7. Mouritsen et al. teach the modified TNFα may be prepared as a fusion protein with GM-CSF (claim 26, 40, 41) (page 7, full paragraph 2; paragraph bridging pages 9-10). Mouritsen et al. teach T cell epitopes derived from tetanus toxin (claims 17, 18) (page 14, line 15). The native form of TNFα is known to be a trimer, as recited in claim 19. Mouritsen et al. describe DNA molecules encoding the modified TNF a molecule, expression vectors comprising the DNA molecules, host cells comprising the vectors, and a recombinant method of producing the modified TNFα molecules, as recited in claims 20-25 (page 8, line 10, through page 9, line 6; page 10, line 8, through page 11, line 12; page 14, lines 13-20; Figure 3). Mouritsen et al. teach a vaccine against TNFα comprising the modified TNFα molecule and calcium phosphate (claims 27, 42) (page 7, full paragraph 2), and injection of the vaccine (claims 27, 32, 47) (page 7, paragraph bridging pages 6-7).

Mouritsen et al. do not teach a modified human TNFα molecule. Pennica et al. (Figure 1), Shirai et al. (Figure 1), or Wang et al. (Figure 4) teach human TNFα molecules and DNA molecules encoding same. Pennica et al., Shirai et al., or Wang et al. do not teach a modified human TNFα molecule for use as a vaccine. However, it would have been obvious to one of

ordinary skill in the art at the time of Applicants' invention make a modified mouse TNFα molecule, as taught by Mouritsen et al., and to modify that teaching by substituting a human TNFα molecule, as taught by Pennica et al., or Shirai et al., or Wang et al., with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because the human protein could be administered as an anti-TNFα vaccine to humans suffering from diseases where TNFα is important for the pathogenesis.

Mouritsen et al. in view of Pennica et al., Shirai et al., or Wang et al. do not teach modifications according to claims 6, 8-16.

Jones et al. teach: the highly flexible loop regions form potential linear epitopes prominently displayed on the surface of the native TNF structure (paragraph bridging pages 109 and 113); the interaction between TNF and its receptor must somehow differ from those required for binding of an antibody to TNF (page 113, full paragraphs 1-2); regions of functional importance for receptor binding (paragraph bridging pages 113-114 through paragraph bridging pages 122 and 124, and the tables and figures therein). Jones et al. do not teach modifications according to claims 6, 8-16. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a modified human TNFα molecule, as taught by Mouritsen et al. in view of Pennica et al., Shirai et al., or Wang et al., and to modify that teaching by substituting a region of functional importance in the TNFα molecule for receptor binding, as taught by Jones et al., with a reasonable expectation of success. One of ordinary skill in the art

would be motivated to make this substitution in these regions because such substitutions would detoxify the recombinant protein. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to select a TNFα B-cell epitope based on the accessability of the region encompassing the epitope in the native protein to the solvent, because these regions must be available to interact react with the antibodies. In so doing one would make a modified human TNFα molecule according to claims 6, 8-16.

Mouritsen et al. in view of Pennica et al., Shirai et al., or Wang et al. further in view of Jones et al. do not teach a modified human TNFα molecule comprising p2 or p30 epitopes.

Panina-Bordigon et al. teach: p2 (15 amino acids) and p30 (21 amino acids) epitopes (page 2238, column 1, full paragraph 1); these epitopes are universally immunogenic and can be recognized in association with a large number of class II molecules (page 2237, column 2, full paragraph 1; page 2238, column 2, full paragraph 3); the fact that p2 and p30 epitopes show a very promiscuous binding to human class II molecules is encouraging for the development of synthetic vaccines that will be active in a large portion of the population (page 2241, paragraph bridging columns 1-2). Panina-Bordigon et al. do not teach a modified human TNFα molecule comprising p2 or p30 epitopes. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a modified human TNFα molecule, as taught by Mouritsen et al. in view of Pennica et al., Shirai et al., or Wang et al., and to modify that teaching by substituting the p2 and/or p30 epitopes, as taught by Panina-Bordigon et al., with a

reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because the fact that p2 and p30 epitopes show a very promiscuous binding to human class II molecules is encouraging for the development of synthetic vaccines that will be active in a large portion of the population. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a p2 (15 amino acids) and p30 (21 amino acids) substitution centered on a region of functional importance in the TNFα molecule for receptor binding, as taught by Jones et al., with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this substitution because substitutions in these regions would detoxify the recombinant protein and it would be adjacent to a TNFα B-cell epitope based on the accessability of the region encompassing the epitope in the native protein to the solvent, because these regions must be available to interact react with the antibodies. In so doing one would make a modified human TNFα molecule according to claims 6, 8-16.

Double Patenting

15. Claims 28, 32, 43, 44, 45, 47 are objected to under 37 CFR 1.75 as being a substantial duplicates of claim 27. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed

claim. See MPEP § 706.03(k). The intended uses of the vaccines do not distinguish the vaccines and they cover the same thing.

16. Applicant is advised that should claim 27 be found allowable, claims 28, 32, 43, 44, 45, 47 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The intended uses of the vaccines do not distinguish thevaccines and thy cover the same thing.

Conclusion

17. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID ROMEO
PATENT EXAMINER

January 15, 2000